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HOWREY LLP
C/O IP DOCKETING DEPARTMENT
2941 FAIRVIEW PARK DRIVE, SUITE 200
FALLS CHURCH, VA 22042-2924

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,484	RIDDER ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37 and 39-51* is/are pending in the application.

4a) Of the above claim(s) *1-32 and 41-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-37,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2003* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed January 3, 2007, is acknowledged and has been entered. Claim 38 has been canceled. Claims 33-35, 39, and 40 have been amended.

2. Claims 1-37 are pending in the application. Claims 1-32 and 41-51 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 21, 2006.

3. Claims 33-37, 39, and 40 are currently under prosecution.

Election/Restrictions

4. Applicant's remarks regarding the restriction and election requirement are acknowledged.

Claim 33 is hereby designated a linking claim, linking the different inventions of Group III (claims 34-40), which are identified in section 4, beginning at page 12 of the Office action mailed June 22, 2006.

Applicant is advised that the restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s). Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the instant application. Applicants are advised that if any such claims depending from or including all the limitations of the allowable linking claims are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also M.P.E.P. § 804.01.

Additionally, the requirement to elect one of the different inventions of Group III (claims 34-40), which are identified in section 4, beginning at page 12 of the Office action mailed June 22, 2006, by specifying the "normalization marker" to which the claims are directed has been withdrawn. As such, claims 34-40 are currently under prosecution to any extent that the claims are directed to the process of claim 33, wherein the normalization marker is selected from the any of those recited in claims 35, 39, and 40.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 8, 2006.

Response to Arguments

6. Applicant's arguments with respect to the grounds of rejection set forth in the preceding Office action mailed September 8, 2006, have been considered but are moot in view of the new ground(s) of rejection.

Specification

7. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Tween™; see the specification at, e.g., paragraph [0047] of the published application[1].

[1] U.S. Patent Application No. 2004/0023288 A1.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 34, 35, 39, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 33-37, 39, and 40 are directed to a process for diagnosing cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia, said process comprising detecting the level of expression $p16^{INK4a}$, detecting the level of expression of a normalization marker characteristic of the presence of ectocervical or endocervical cells, determining the adequacy of the sample *based on* the level of the normalization marker detected, and diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia *based on* the levels of $p16^{INK4a}$ and the normalization marker (italics and underscoring added for emphasis).

Claims 33-37, 39, and 40 are indefinite for the following reasons:

(1) Although the claims are directed to a process for a process for diagnosing cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia, according to the body of the claim the process comprises the step of diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia. Notably cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia are distinct conditions or diseases; accordingly, one would not diagnose the same condition or disease as cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia. Rather, one would

diagnose the condition or disease as cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia. Nevertheless, because of the apparent incongruity of the language of the claims, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the necessary degree of clarity and particularity to meet the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(2) The claims are directed to an active process that comprises determining the adequacy of the sample based upon *on* the level of the normalization marker detected and then diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia *based on* the levels of $p16^{INK4a}$ and the normalization marker, but it cannot be determined how these determinations and diagnoses are necessarily "based" on the level of the normalization marker and/or $p16^{INK4a}$. As such, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the necessary degree of clarity and particularity to meet the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(b) Claims 34, 35, 39, and 40 are further indefinite because the claims use of one or more of the designations "$p16^{INK4a}$", "p14ARF", "gamma-catenin", "Ep-Cam", "E-cadherin", "alpha-catenin", "beta-catenin", Involucrin", "CK8", "CK18", "CK10", "CK13", and "p120" as the sole means of identifying the polypeptides to which the claims refer. The use of such designations only to identify the particular polypeptides renders the claims indefinite because different laboratories may use the same designations to refer to completely distinct polypeptides. Furthermore, while the specification may provide some guidance as to which polypeptide is identified using the nomenclature of the claims, it cannot be determined if the claims should be limited to any polypeptide having any one of the above-mentioned designations, or if the claims are to be limited to only one particular polypeptide. For example, the specification discloses that the term "p120" identifies a polypeptide having the amino acid sequence set forth as Swiss

Protein Database Accession No. O60716, which is otherwise known as "p120 catenin" (see, e.g., page 29, Table 3); yet, the art teaches that the designation "p120" or "p120 catenin (p120ctn)" identifies a plurality of discrete members of a genus of proteins, which owing to alternative splicing and multiple translation initiation codons, includes several isoforms that are expressed from a single gene, which share the central Armadillo repeat domain but have divergent N- and C-termini; see, e.g., Aho et al. (*J. Cell Sci.* 2002 Apr 1; **115** (Pt 7): 1391-1402)[2]. It is not evident to which, if any, of these different isoforms the claims are necessarily directed. Accordingly, Applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

For this reason, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the necessary degree of clarity and particularity to meet the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

Because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide, it is therefore suggested that this issue be remedied by amending the claims to include the amino acid sequence of the polypeptides by references to specific sequence identification numbers of the corresponding amino acid sequences, as set forth in a Sequence Listing.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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[2] Incidentally, Aho et al. teaches little is known about the biological functions of the different isoforms (abstract).

11. Claims 34, 35, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

"Guidelines" states that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

The claims are directed to a process comprising the active steps of detecting the level of at least one "relevant marker characteristic for the presence of cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia in humans" and "normalization marker characteristic for the presence of ectocervical or endocervical cells".

Without possession of these *markers* and means for detecting their levels, the process cannot be practiced; and absent a detailed and particular description of the markers, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention.

More particularly, the claims are directed to one or more polypeptides (i.e., *markers*) identified by the designations "$p16^{INK4a}$", "p14ARF", "gamma-catenin", "Ep-Cam", "E-cadherin", "alpha-catenin", "beta-catenin", Involucrin", "CK8", "CK18", "CK10", "CK13", and "p120". However, as explained in the above rejection of the claims under 35 U.S.C. § 112, second paragraph, because of the use of such nomenclature alone, it cannot be determined to which particular polypeptide(s) the claims are directed.

As explained in greater depth in the following paragraphs, it is presumed that the claims are directed to more than one genus of polypeptides having a designation set forth in the claims, which includes members having substantially differing structures and/or functions.

This position is supported, for example, by Aho et al. (supra), teaching that the designation "p120" or "p120 catenin (p120ctn)" identifies a plurality of discrete members of a genus of proteins, which owing to alternative splicing and multiple translation initiation codons, includes several isoforms that are expressed from a single gene, which share the central Armadillo repeat domain but have divergent N- and C-termini; see entire document (e.g., the abstract). Aho et al. further teaches, though little is known about their specific functions, these structural variants are expected to have non-redundant and quite possible unique roles in cellular biology; see, e.g., the abstract; and page 1391, column 1. Additionally, Aho et al. teaches these variants are differentially expressed in different types of tissues and different types of cells; see, e.g., the abstract.

Following the example provided by the disclosure of Aho et al. it is submitted that it is apparent that the skilled artisan cannot predict whether any one of the presumably different members of polypeptides (e.g., "p120") to which the claims are directed will be suitable for use in practicing the claimed process because the artisan cannot know whether any species of polypeptide encompassed by the claims will be expressed by the cervical epithelium, or more particularly by the endocervix or ectocervix. Accordingly, the artisan cannot know whether any one species of polypeptide encompassed by the claims can be used as an appropriately suitable normalization marker to identify the presence of endocervical and/or ectocervical cells, or distinguish such cells from other cervical or non-cervical cells, so as to determine the adequacy of the sample. More pointedly, the description is not sufficiently details to permit the skilled artisan to immediately envision, recognize or distinguish which polypeptides encompassed by the claims can be used to practice the claimed process; and therefore the suitability of any such polypeptide for use as a normalization marker in practicing the claimed invention can only be determined empirically.

For these reasons, because of the apparent differences in the breadth of the claims and breadth and particularity of the disclosure, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention as the time the application was filed.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes with the requisite particularity the polypeptides to which the claims are directed, which can be used in practicing the claimed invention to achieve the claimed diagnostic result. A description of what a material does, or what is must be capable of doing, rather than of what it is, does not suffice to describe the claimed invention.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). Again, the suitability of any species of polypeptide for use as a normalization marker in practicing the claimed invention can only be determined empirically.

Finally, "Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of polypeptides, which are reasonably presumed to vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying

characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

12. Claims 33-37, 39, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a process for diagnosing cervical dysplasia or cervical cancer, said process comprising detecting the level of expression $p16^{INK4a}$, **does not reasonably provide enablement for using** a process for diagnosing any type of cervical intraepithelial neoplasia, said process comprising detecting the level of expression $p16^{INK4a}$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The claims are directed to a process for diagnosing cervical dysplasia, cervical intraepithelial neoplasia and cervical cancer, said process comprising detecting the level of expression $p16^{INK4a}$, which according to claim 33 is a "marker characteristic for the presence of cervical dysplasia, cervical cancer, and cervical intraepithelial neoplasia".

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Although the claims are directed to a process for a process for diagnosing cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia, cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia are distinct conditions or diseases; accordingly, one would not reasonably expect to use the process to diagnose the same condition or disease as cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia. Rather, at best, one might expect to diagnose the condition or disease as cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia.

Furthermore, if as the claim reads, $p16^{INK4a}$ is a "marker characteristic for the presence of cervical dysplasia, cervical cancer, **and** cervical intraepithelial neoplasia", it cannot be determined how the active step of diagnosing cervical dysplasia, cervical cancer **or** cervical intraepithelial neoplasia *based on* the levels of $p16^{INK4a}$ and the normalization marker is to be achieved. A marker that does not distinguish cervical dysplasia, cervical cancer, and cervical intraepithelial neoplasia cannot be expected to be useful in the differential diagnosis of such conditions or diseases.

In addition, it is aptly noted that while the claims are directed to an active process that comprises determining the adequacy of the sample based upon *on* the level of the normalization marker detected and then diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia *based on* the levels of $p16^{INK4a}$ and the normalization marker, the claims fail to make it clear how the determination and diagnosis are "based" on the level of the normalization marker and/or $p16^{INK4}$; and therefore it is submitted that the claims fail to describe the process that is regarded as the invention in such a clear and particular manner to reasonably enable the skilled artisan to practice the claimed

invention. Moreover, the artisan would not know how the invention is necessarily practiced, as intended, to diagnose cervical dysplasia, cervical cancer and cervical intraepithelial neoplasia in humans.

Finally, with further regard to the claimed process, inasmuch as it is allegedly useful for diagnosing cervical intraepithelial neoplasia, Klaes et al. (*Int. J. Cancer.* 2001 Apr 15; **92** (2): 276-284) (of record; cited by Applicant) teaches the marked overexpression of $p16^{INK4a}$ in all specimens of cervical intraepithelial neoplasm (CIN) I lesions (n = 47) *except* those associated with low-risk HPV types; see entire document (e.g., the abstract). Moreover, although Klaes et al. teaches cervical dysplastic cells, CIN II and CIN III lesions, and cervical carcinoma cells could be identified in the specimens using an antibody that specifically binds $p16^{INK4a}$, no detectable expression as observed in normal cervical epithelium or low-grade cervical lesions (CIN I) associated with low-risk HPV types; see, e.g., the abstract. Accordingly, contrary to the allegations set forth in the specification, there is factual evidence the claimed process cannot be used to diagnose any type of cervical intraepithelial neoplasia, but rather only those types of CIN not associated with low-risk HPV.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said

subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 33, 34, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bibbo et al. (*Acta Cytologica.* 2002 Jan-Feb; **46** (1): 25-29) and Grundhoefer et al. (*Cytometry*. 2001 Dec 15; **46** (6): 340-344).

Claims 33, 33, 36, and 37 are drawn to an active process comprising preparing a sample solution from a human cervical sample, detecting the level of at least one relevant marker characteristic for the presence of cervical dysplasia, cervical cancer, and cervical neoplasia in human, wherein said at least one relevant marker is $p16^{INK4a}$, detecting the level of at least one normalization marker characteristic for the presence of ectocervical or endocervical cells, determining that the sample is adequate if detectable levels of the normalization marker are present in the sample, and if adequate, diagnosing cervical dysplasia, cervical cancer or cervical intraepithelial neoplasia if detectable levels of $p16^{INK4a}$ are present.

Although claim 36 recites, "wherein the method is used in the early detection or primary screening tests of cervical lesions", the claim is nevertheless drawn to the method of claim 33, and thus the recitation only serves to further limit the manner in which the claimed process is intended to be used. So, in terms of this rejection, it is of no consequence that the prior art does not teach the use of the claimed process in any particular context, so long as the disclosed process is materially and manipulatively indistinguishable from the claimed process.

Bibbo et al. teaches a procedure for immunocytochemical detection of $p16^{INK4a}$ in thin-layer, liquid based specimens; see entire document (e.g., the abstract). Bibbo et al. teaches the procedure comprises the step of preparing a sample solution from a human cervical sample; see, e.g., page 25, column 1. Bibbo et al. teaches the level of expression of $p16^{INK4a}$ was then assessed; see, e.g., page 25, column 2. By comparing the results of the assessment to the results of previous diagnoses, Bibbo et al. concludes that $p16^{INK4a}$ may be used as a surrogate diagnostic marker of cervical neoplasia; see, e.g., page 26, column 1. Notably Bibbo et al. discloses that the biopsy negative for $p16^{INK4a}$ corresponded to a positively staining ThinPrep™ with a diagnosis

of high-grade squamous intraepithelial lesion (HSIL), suggesting that sampling error may have been responsible for the negative staining result (page 27, column 1; and page 29, column 1).

Although Bibbo et al. does not expressly teach determining the adequacy of the cervical tissue specimen for the diagnostic procedure, Bibbo et al. remarks that the false negative results was likely due to a sampling error; accordingly, Bibbo et al. suggests that a determination of the adequacy of the cervical tissue specimen for the diagnostic procedure could help to eliminate false negative results.

Grundhoefer et al. teaches the need to determine the adequacy of cervical tissue specimens for use in diagnostic procedures; see entire document (e.g., the abstract; and page 340, columns 1 and 2). Grundhoefer et al. teaches cervical cancer screening involves morphological assessment of a heterogeneous population of cells, including ectocervical cells, endocervical cells, polymorphonuclear leukocytes, and lymphocytes (page 340, column 2). Grundhoefer et al. teaches the adequacy of a cervical cytology specimen is defined by determinations in the specimen of the presence of both ectocervical and endocervical cells, providing evidence that the transformation zone has been sampled (page 340, column 2). Grundhoefer et al. describes a process for determining the adequacy of liquid-based cervical cytology specimens; see entire document (e.g., the abstract). Grundhoefer et al. teaches the ectocervical and endocervical cells are distinguished by measuring the level of expression CAM 5.2 and light scatter using flow cytometry; see, e.g., page 342, column 1; and page 343, Figures 2 and 3.

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to practice the diagnostic procedure disclosed by Bibbo et al. by including in the process the step by which the adequacy of the specimen is assessed by a determination of the level of expression of a "normalization marker" (e.g., CAM 5.2), which characterizes the presence in the specimen of endocervical (columnar) or ectocervical (squamous) cells, thereby marking the presence in the sample of an adequate component of endocervical cells and/or ectocervical cells. One ordinarily skilled in the art at the time of the invention would have been motivated to do

so to practice the diagnostic procedure as effectively as possible by determining the adequacy of the specimens and thereby helping to eliminate the occurrence of false negative results that might otherwise be achieved using inadequate, unsatisfactory ("UNS") or satisfactory by limited by ("SBLB") specimens, such as specimens lacking an endocervical or ectocervical component.

15. Claims 35, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bibbo et al. (*Acta Cytologica*. 2002 Jan-Feb; **46** (1): 25-29) and Grundhoefer et al. (*Cytometry*. 2001 Dec 15; **46** (6): 340-344), as applied to claims 33, 34, 36, and 37 above, and further in view of Levy et al. (differentiation. 1988 Dec; 39 (3): 185-196).

Claims 35, 39, and 40 are drawn to the process of claim 33, wherein the normalization marker is CK13 or CK18.

Bibbo et al. and Grundhoefer et al. teach that which is set forth in the above rejection of claims 3, 34, 36, and 37 under 35 U.S.C. 103(a).

However, neither Bibbo et al. or Grundhoefer et al. expressly teaches determining the adequacy of the cervical tissue specimen for the diagnostic procedure by determining the level of expression of CK13 or CK18 to assess the presence in the sample of an endocervical component, as is mandated by the Bethesda System (TBS), which provides the criteria for use in determining the adequacy of specimens.

Nonetheless, Levy et al. teaches subtyping of epithelial cells of normal and metaplastic human cervical tissue using antibodies that specifically bind to cytokeratins CK13 and CK18; see entire document (e.g., the abstract). More particularly, Levy et al. teaches their results indicate that an analysis of the expression of the these cytokeratins by cervical tissue specimens can distinguish between at least four types of cells residing within the simple epithelium of the endocervix, namely columnar non-cilitated cells, ciliated cells, and two populations of reserve cells; see, e.g., the abstract. Levy et al. suggest, since metaplasia was positively stained by antibodies that specifically bind to these cytokeratins, the endocervical reserve cells that express CK13 are most probably the cells from which endocervical metaplasia is derived (abstract).

Accordingly, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to practice the diagnostic procedure disclosed by Bibbo et al. by including in the process the step by which the adequacy of the specimen is assessed by a determination of the level of expression of CK13 and/or CK18, thereby marking the presence in the sample of an adequate component of endocervical (columnar) cells. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to practice the diagnostic procedure as effectively as possible by determining the adequacy of the specimens and thereby helping to eliminate the occurrence of false negative results that might otherwise be achieved using inadequate, unsatisfactory ("UNS") or satisfactory by limited by ("SBLB") specimens, such as specimens lacking an endocervical component. Day et al. teaches the impact of the absence of endocervical cells upon the adequacy of the specimen.

Conclusion

16. No claim is allowed.

17. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Kimmig et al. teaches cytokeratin labeling can optimize the analysis of specimens of cervical cancer. Litvinov et al. (of record) teaches EpCAM expression differentiates different types of cervical cells. von Knebel Deobertiz. (Dis. Markers. 2001; 17 (3): 123-128) teaches p16INK4a is a diagnostic marker of cervical dysplasia and cancer. Martens et al. teaches keratin 8 and 17 are of diagnostic value in cervical cytology. Smedts et al. teaches changing patterns of keratin expression during the progression of CIN. Davey et al. reviews current laboratory practices related to the assessment of cervical specimen adequacy.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

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